REMARKS

The Amendments to the Specification

Applicants have amended the specification to update the status of the priority application. Specifically, this application is a continuation-in-part (CIP) of U.S. Patent Application 09/129,028, filed August 4, 1998, now issued as U.S. patent 7,790,669.

The Claim Amendments

Applicants have amended claims 1, 2, 5, 33, 63, 65, 66 and 70-72; and canceled claim 73. Applicants previously canceled claims 3-4, 9-32, 34-62 and 67-69. After entry of this amendment, claims 1, 2, 5-8, 33, 63-66 and 70-72 will remain pending in this application.

Applicants have amended claims 1, 2, 5, 33, 63, 65, 66 and 70 to delete "a functional fragment thereof comprising $CysX_7CysK_4CysX_{10}CysXCysX_8Cys$ (SEQ ID NO: 1)". These claims and claims that depend from them now refer to a composition comprising a TGF-α polypeptide. These amendments are supported, for example, by former claims 1, 2, 5, 33, 63, 65, 66 and 70.

Applicants have also amended claims 1, 2, 33, 63, 65, 66 and 70 to recite that the claimed method is evidenced by and results in an amelioration of behavioral deficits attributable to the damage or lesion. These amendments are supported, for example, in the application at page 4, line 22 to page 5, line 8.

Applicants have also amended claims 71 and 72 to improve their form.

Applicants' cancellation of subject matter by amendment herein is specifically without waiver of applicants' rights to file divisional or continuing applications directed to this subject matter and claiming the benefit of and priority to this application.

The June 2, 2010 Non-final Office Action

35 U.S.C 119(e): Priority

The Examiner argues that applicants allegedly have not complied with one or more conditions for receiving the benefit of an earlier fling date under 35 U.S.C. 119(e). According to the Examiner, former claims 1, 2, 5-8, 33, 63-66 and 70-72 are not entitled to the benefit of the August 4,1997 filing date of the U.S. provisional application 60/055,383 (the '383 provisional application), because the sequence $CysX_7CysK_4CysX_{10}CysXCysX_8Cys$, as recited in those claims, was not recited in the '383 provisional application. The Examiner contends that the sequence was first recited in the U.S. patent application 09/129,028 (the '028 application, now US patent 7,790,669), filed August 4, 1998. On that basis, the Examiner contends that former claims 1, 2, 5-8, 33, 63-66 and 70-72 are only entitled to the benefit of the August 4, 1998 filing date of the '028 application.

Amended claims 1, 2, 5, 33, 63, 65, 66 and 70 and the claims that depend from them (i.e., claims 6-8, 64, 71 and 72) are entitled to the benefit of the August 7, 1997 filing date of the '383 provisional application. As discussed above, applicants have amended former claims 1, 2, 5, 33, 63, 65, 66 and 70 to delete "a functional fragment thereof comprising $CysX_7CysK_4CysX_{10}CysXCysX_8Cys$ (SEQ ID NO: 1)". As amended, claims 1, 2, 5, 33, 63, 65, 66 and 70 and thus, the claims depending from them (i.e., claims 6-8, 64, 71 and 72) no longer recite the above sequence. They refer only to a TGF-α polypeptide, which was recited in the '383 provisional application. Thus, claims 1, 2, 5-8, 33, 63-66 and 70-72 are entitled to an effective filing date of August 4, 1997, the filing date of the '383 provisional application. Applicants request that the Examiner reconsider priority in view of the claim amendments.

35 U.S.C. §102(b): Anticipation

The Examiner has rejected former claims 1, 2, 5-7, 33, 63-64 and 70-72 as allegedly lacking novelty under 35 U.S.C. § 102(b) over Alexi (Alexi et al., Neuroscience, 78(1):73-86, 1997). According to the Examiner, the priority date for the rejected claims is August 4, 1998, the filing date of the '028 application. As a result, the Examiner argues that Alexi, published in May 1997, anticipates the claims under 35 U.S.C. § 102(b) "for the reasons of record in the previous Office Action" (Office Action page 4).

Alexi was cited in the March 28, 2008 non-final Office Action ("the previous Office Action") in a 102(a) rejection (now withdrawn). In that March 28, 2010 Office Action, the Examiner argued that Alexi allegedly reports the intrastriatal administration of TGF-α to animals at the site of unilateral intrastriatal quinolinic acid lesion, and that Alexi's method alleged led to a marked increase of cells. The Examiner further argued that, although Alexi did not identify these cells as neural progenitor cells, "the effect of identical modes of administration of an identical polypeptide would lead to the inherent claimed effect of 'migration of the neural progenitor cell or progeny thereof to the site'" (March 28, 2008 Office Action, page 12, paragraph 9). On these alleged bases, the Examiner then argued that Alexi destroyed the novelty of former claims 1, 2, 5-7, 33, 63-64 and 70-72. As discussed below, applicants' claim amendments overcome this novelty rejection.

As discussed above, applicants have amended former claims 1, 2, 5, 33, 63, 65, 66 and 70 (and the claims that depend therefrom) to delete the recitation "a functional fragment thereof comprising $CysX_7CysK_4CysX_{10}CysXCysX_8Cys$ (SEQ ID NO: 1)". As amended, claims 1, 2, 5, 33, 63, 65, 66 and 70 and the claims depending from them (i.e., claims 6-8, 64, 71 and 72) are entitled to an effective filing date of August 4, 1997, the filing date of '383 provisional application. Alexi was published in May 1997, which is less than a year prior the effective filing date of amended claims 1, 2, 5, 6-8, 64, 71 and 72. Thus, Alexi does not anticipate these amended claims under 35 U.S.C. § 102(b). Alexi also

does not anticipate any of the amended claims under 35 U.S.C. § 102(a) because the claimed subject matter was conceived in March 1997, as the Examiner acknowledged in the present Office Action (See Office Action, page 4). For all of the above reasons, amended claims 1, 2, 5-8, 33, 63-66 and 70-72 are novel over Alexi.

35 U.S.C. §103(a): Obviousness

Claims 1, 2, 5-8, 33, 63-66 and 70-73 stand rejected under 35 U.S.C. § 103 over Weiss (US patent 5,980,885, of record) in view of Kelly (Kelly et al., Brain Research, 94(3): 507-522, 1974). As discussed in detail below, the amended claims are not obvious over Weiss and Kelly. Indeed, the methods of the amended claims are selection inventions over the cited documents alone or in combination. Applicants respectfully request entry of the amendments and allowance of the amended claims.

(i) Introduction

The amended claims are directed to methods of attracting a neural progenitor cell, or a progeny thereof, to a site of damage or lesion in a CNS tissue comprising administration of a TGF-α polypeptide to a subject having CNS damage or lesion, said administration being outside of the ventricles and to a location selected from the group consisting of the striatum, pallidum, septum, cortex, external capsule, internal capsule, substantia nigra-ventral tegmentum, and at or adjacent to an ependymal or subependymal zone (hereinafter "extra-ventricular").

Dr. James Fallon, one of the named co-inventors of this application, has studied growth factors, including EGF, TGF-α; TGF-β and FGF for decades, and his research has focused on TGF-α since 1982. In fact, Dr. Fallon's discoveries began all research on growth factors in the brain, those studies being spurred by Dr. Fallon's discovery in 1984 that EGF was expressed in the mammalian brain -the first report that any growth factor was expressed in the brain. Dr. Fallon's discovery was so fundamental that it was published in the journal *Science*. *See* Fallon *et al.*, "Epidermal Growth Factor Immunoreactive Material

in the Central Nervous System: Location And Development," *Science* 224: 1107-1109 (1984); *see also* Fallon Declaration filed May 5, 2009 ("Fallon I Declaration") at ¶ 5 (copy attached as Exhibit I).

Dr. Fallon's lab at the University of California (Irvine) was also the first to show that administration of TGF-α in the presence of an injury signal can reverse loss of motor function in a neurological injury model. Dr. Fallon published a report of those studies in the *Proceedings of the National Academy of Sciences*. *See* Fallon, *et al.*, "In vivo induction of massive proliferation, directed migration, and differentiation of neural cells in the adult mammalian brain," Proc. Natl. Acad. Sci. 26(97): 14686-14691 (2000) ("the Fallon 2000 PNAS paper" (previously submitted)); *see also* Fallon I Declaration at ¶ 7-8.

Dr. Fallon's 2000 PNAS paper was cited in a 2001 Stem Cell Report prepared by NIH for Congress, as the study showing proof of concept for adult stem cell treatment for neurological disorders. *See* Report Prepared by the National Institutes of Health, "Stem Cells: Scientific Progress and Future Research Directions," June 2001, at page 84 (previously submitted); *see also* Fallon I Declaration at ¶ 9.

(ii) Weiss Even When Combined With Kelly Does Not Render The Amended Claims 1, 2, 5-8, 33, 63-66 and 70-73 Obvious Under 35 U.S.C. § 103

The amended claims are not obvious over Weiss and Kelly, alone or in combination. Indeed, the amended claims represent an unobvious selection over the cited documents. And, that selection is characterized by unexpected and surprising results. Further, there is nothing in any of Weiss or Kelly that would have motivated or suggested to the skilled worker the surprising effects of: (1) a TGF-α polypeptide, (2) its administration to a subject having CNS damage or lesion outside of the ventricles and to a location selected from the group consisting of the striatum, pallidum, septem, cortex, external capsule, substantia nigra-ventral tegmentum and at a site adjacent to an ependymal

and subependymal zone or (3) the combination of the two. The amended claims are directed to methods characterized by all three. For that reason alone, these claims are not obvious over the cited documents.

To establish a *prima facie* case of obviousness some reason must be identified that would have led one of ordinary skill in the art to pursue a claimed species. *See Takeda Cham. Indus, v. Alphapharm Pty, Ltd.*, 492 F.3d 1350, 1356 (Fed. Cir. 2007); *Eisai Co. v. Dr. Reddy's Labs., Ltd.*, 533 F.3d 1353,1359 (Fed. Cir. 2008) ("In other words, post-*KSR*, a *prima facie* case of obviousness for a chemical compound still, in general, begins with the reasoned identification of a lead compound.").

The amended claims recite three inventive selections over Weiss and Kelly: (1) the use of **TGF-α** to treat neurological injuries; (2) the administration of the TGF-α outside of the ventricles and to a location selected from the group consisting of the striatum, pallidum, septem, cortex, external capsule, substantia nigra-ventral tegmentum and at a site adjacent to an ependymal and subependymal zone; and (3) the **combination** of TGF-α and that extra-ventricular administration. None of Weiss or Kelly suggested any of such selections. And, none of them suggested the unexpected results that the methods of applicants' amended claims achieve: an amelioration of behavioral effects of neurological diseases and injuries.

(A) TGF-α

Applicants selected one trophic factor, TGF-α, from the many possible growth factors and combinations of growth factors referred to in Weiss. *See e.g.*, Weiss at col. 15, line 60 - col. 16, line 23;[1] col. 17, lines 9-14; col, 19, lines 29-43; col, 20, line 65 to col, 21, line 9; and col. 25, lines 41-55. Although TGF-α is mentioned in Weiss, Weiss places no particular emphasis on TGF-α (e.g., col. 15, line 60 – col. 16, line 23[2]; col. 19, lines 29-43;

[1] This passage of Weiss appears in a section entitled "In Vitro Proliferation of Neural Stem Cells."

[2] The cited section (col 15-16) of Weiss which states that "[p]referred proliferation – inducing growth factors include EGF and TGFα," is a section discussing factors to be used in supplementing culture medium *in vitro*.

and col. 25, lines 41-55), nor does Weiss describe any *in vitro* or *in vivo* experiments or *in vitro* assays using TGF-α. In fact, when Weiss refers to the effects of various growth factors on proliferation and neurosphere production, Weiss does not include TGF-α among the tested factors. *See* Weiss at Table II (col. 56). Weiss' specific examples of administration of growth factors *in vivo* feature only FGF, EGF, or a combination of EGF and FGF. *See* Weiss at col. 46-49, Examples 27-31; Weiss at col. 17, lines 9-14.

Kelly does not remedy the deficiencies of Weiss. The Examiner points to Kelly solely to show that "methods comprising direct intrastriatal injection via sterotaxic coordinates were recognized within the prior art". See Office Action, page 7. Kelly does not refer to TGF-α or its functional fragment anywhere.

Against this backdrop of no blazemarks pointing to TGF-α or suggesting that it has any special properties or effects in cell proliferation, neurogenesis and the resulting amelioration of behavioral effects of neurological disorder or injury, applicants have surprisingly discovered and demonstrated that TGF-α alone, among all of the many Weiss growth factors, induces significant and useful progenitor cell proliferation and directed migration to the site of neurological injury and leads to an amelioration of behavioral effects attributable to the injury or damage.

In particular, applicants have demonstrated that the actual growth factors used in Examples 27-31 of Weiss (EGF and FGF) do not cause that proliferation or migration and do not lead to applicants' results in an amelioration of behavioral effects attributable to the injury. For example, in the Fallon I Declaration, at ¶ 16, Dr. Fallon summarized his experiments which showed that intrastriatal administration of EGF did not induce sustained cell proliferation or migration and did not lead to any recovery of motor deficits in the 6-OHDA Parkinson's disease model. In the Fallon I Declaration, Dr. Fallon also summarized his experiments which showed that the administration of growth factors, including TGF-α , EGF, FGF, BDNF, NGF, GDNF, NT3 and NT4, alone or in combination, to the lateral ventricles of both unlesioned and lesioned rats did not induce significant cell proliferation or neurogenesis of functional neurons. See Fallon I Declaration at ¶¶ 27-31. And, Dr.

Fallon reported that no behavioral improvement was observed in the treated lesioned animals. *See* Fallon I Declaration, ¶ 32. There is but one conclusion: TGF-α is unexpectedly different from other Weiss's growth factors in its ability to induce cell proliferation, migration, neurogenesis and an amelioration of behavioral effects attributed to neurological injury.

Applicants also submit Dr. Fallon's actual data from his experiments. See Fallon II Declaration and Exhibits A to E, as filed in the '028 application (now the '669 patent) on May 11, 2010.

In the Fallon II Declaration, Dr. Fallon reports on two sets of experiments. In the first set of experiments (ones that correspond to those summarized in ¶¶ 27-32 of the Fallon I Declaration), Dr. Fallon reports treating, both unlesioned and lesioned rats (6-OHDA model of Parkinson's disease), using ICV (intracerebroventricular) administration and eight (8) individual growth factors (EGF, TGF-α, bFGF (also known as FGF-2), aFGF (also known as FGF-1), GDNF, NGF, NT3 and NT4 and three (3) combinations of growth factors (TGF-α/FGF, EGF/FGF, and GDNF, TGF-β, NT3 and NT4). See Fallon II Declaration at ¶¶ 3-6)

In the Fallon II Declaration, Dr. Fallon also reports the results of those experiments. In none did he observe any significant cell proliferation ("no signif prolif"). See Fallon II Declaration at ¶¶ 7-11 and Exhibits A and B. At best, the ICV administration of TGF-α to lesioned rats induced a cell proliferation in the order of a few tens of cells, a number far too low to have any biological effects. See Fallon II Declaration at ¶ 10. Finally, in the Fallon II Declaration, Dr. Fallon reported that in none of these growth factor--ICV experiments did he observe any behavioral improvement as the result of the ICV administration of these diverse growth factors, including the ones specifically used in the Weiss examples (EGF, FGF and EGF/FGF). See Fallon II Declaration, ¶ 12.

In the second set of experiments reported in the Fallon II Declaration, Dr. Fallon administered five individual growth factors (TGF-α, EGF, aFGF (FGF-1), bFGF (FGF-2) and NGF) intrastriatally to lesioned animals (6-OHDA model). See Fallon II Declaration

at ¶ 15. In the Fallon II Declaration, Dr. Fallon also reported the results of those treatments: only TGF-α led to significant and useful cell proliferation, cell migration and behavioral improvement. See Fallon II Declaration, ¶¶ 16-21 and 23, and Exhibits C and D and the Fallon 2000 PNAS paper. Indeed, except for TGF-α, Dr. Fallon observed, at best, in actual photographs of his experiments only in the order of tens of cells after intrastriatal administration of the other growth factors (including EGF and FGF, specifically used by Weiss). See Fallon II Declaration at ¶ 18 and Exhibit C. By contrast, Dr. Fallon conservatively estimated that TGF-α induced 1 million cells using intrastriatal administration with the identical 6-OHDA model. His calculations actually suggested far more. See Fallon II Declaration, ¶ 23 and Exhibit E.

The Guerra Crespo Neuroscience paper, which is enclosed herewith as Exhibit F, reports similar results using TGF-α and a chronic stroke model. In that paper, Dr. Fallon and his co-authors reported that the intrastriatal administration of TGF-α to lesioned rats (middle cerebral artery occlusion (MCAD) stroke model) induced a massive proliferation response, even when the TGF-α was administered as late as 4 weeks after the injury See Abstract and p. 471-474. Most importantly, Dr. Fallon and his co-workers showed that the TGF-α induced cell proliferation and migration resulted in statistically significant behavioral recovery. See p. 474-475.

The bottom line from these two sets of experiments, as well as the results reported in the Fallon 2000 PNAS paper and the Guerra Crespo Neuroscience paper is that only TGF-α, not any of the many other growth factors, referred to in Weiss, and in particular, not the specifically exemplified growth factors used in the Weiss examples (EGF and FGF), is useful in inducing cell proliferation, directed migration and ameliorating behavioral effects attributable to neurological injury and damage. For this reason alone, the amended claims are patentable, and not obvious, over Weiss and Kelly.

(B) Site of administration

There is a second reason why the amended claims are patentable, and not obvious, over Weiss and Kelly--the site of administration. From the many possible sites of administration referred to in Weiss (*see*, e.g., col. 25, line 41-col. 26, line 15), applicants selected and have claimed a site of administration outside of the ventricles and at a location selected from the group consisting of the striatum, pallidum, septem, cortex, external capsule, substantia nigra-ventral tegmentum and at a site adjacent to an ependymal and subependymal zone.

As demonstrated above in Dr. Fallon's actual experiments, TGF-α and other growth factors, and in particular the growth factors specifically exemplified in Weiss (EGF and FGF), did not lead to significant proliferation or migration of cells or any improvement in behavior or function when administered to the site actually exemplified in Weiss: the ICV (i.e., the ventricles). Based on those results, the skilled worker would have had no expectation, much less a reasonable expectation, that those growth factors would induce cell proliferation, migration and amelioration of behavior effects attributable to neurological injury and damage when administered outside of the ventricles and particularly at a location selected from the group consisting of the striatum, pallidum, septem, cortex, external capsule, substantia nigra-ventral tegmentum and at a site adjacent to an ependymal and subependymal zone. Indeed, as shown in Dr. Fallon's second set of experiments, the skilled worker's expectation that none of those growth factors would lead to cell proliferation, migration and amelioration of the behavioral effects attributable to the CNS injury when administered outside the ventricles (e.g., the striatum) was correct. By contrast, as Dr. Fallon has shown, TGF-α when administered outside of the ventricles surprisingly and unexpectedly induces massive cell proliferation, cell migration and amelioration of behavior deficits.

Kelly does not remedy the deficiencies of Weiss. Kelly uses intrastriatal administration of 6-OHDA to induce striatal lesions, not to treat the lesions. In fact, Kelly

administered the treatment (in this case, amphetamine and apomorphine) intraperitoneally into the lesioned animals. See, e.g., Summary on p. 507 and Methods on p. 509. Thus, in view of Kelly, a skilled worker would have no guidance or motivation to administer a treatment composition (such as TGF-α) outside of the ventricles of a lesioned animal. Nor would the skilled worker have any expectation that such extra-ventricular administration would attract neural progenitor cells or progenies thereof to a site of CNS damage/lesion, induce massive cell proliferation, cell migration and amelioration of behavior deficits.

Accordingly, neither of Weiss and Kelly, separately or in combination, makes obvious applicants' amended claims. Therefore, for this reason also -- the site of administration (i.e., extra-ventricular administration of TGF-α) -- the amended claims are patentable and not obvious over any of Weiss and Kelly, alone or in combination.

(C) Combination

A third reason why the amended claims are not obvious over Weiss and Kelly is that none of these documents suggests or teaches the combination of TGF-α and extra-ventricular administration. As demonstrated above, this claimed combination leads to the claimed proliferation, migration, neurogenesis and amelioration of biological effects attributable to the neurological injury or damage.

The only combinations specifically referred to in Weiss are ICV administration and EGF or FGF. Applicants have demonstrated by actual experiments that neither lead to the necessary cell proliferation, migration or most importantly an amelioration of injury. Only applicants' claimed combination is successful.

Kelly does not remedy the deficiency of Weiss. As discussed above, Kelly does not mention TGF-α at all. Nor does it refer to extra-ventricular administration of a treatment (such as TGF-α) to treat CNS lesions or damage. Thus, it could in no way teach or suggest the combination of TGF-α and its extra-ventricular administration.

For this reason also then, applicants' claims are not obvious over Weiss and Kelly.

(D) The work of others supports the unobviousness of the amended claims.

The surprising and unexpected nature of the beneficial effects which applicants obtained following their combination of the extra-ventricular administration and TGF-α, as recited in the amended claims, is further supported by the published results of researchers at the Salk Institute, and further work by Reynolds. These reports confirm that when EGF is administered *in vivo* in the ventricles, according to the methods of Weiss, EGF fails to stimulate the production of neurons. The Salk researchers reported that "progenitor populations in the adult rodent brain respond, in part, differently from the way they respond to administration of mitogens *in vitro*." and noted that although progenitors cultured in the presence of EGF proliferate and differentiate into neurons and glia *in vitro*, EGF has "an unexpected limiting effect on the generation of neurons" *in vivo*. See Kuhn *et al.*, Epidermal Growth Factor and Fibroblast Growth Factor-2 Have Different Effects on Neuronal Progenitors in the Adult Rat Brain, J. Neurosci 17(15):5820-29 at 5828 ("Kuhn"), which is enclosed herewith as Exhibit G. Kuhn further observed that their finding of no new cells of a neuronal phenotype following intraventricular infusion of EGF contrasted in part with the report in Craig et al., 1996 (co-authored by Weiss) that newborn cells of a neuronal phenotype were obtained after administration of EGF. Kuhn at page 5827. Reynolds later confirmed Kuhn's observations when his group reported that *in vivo* administration of EGF into the ventricles failed to convert progenitor cells into stem cells. *See* Louis *et al.* (B.A Reynolds is the last author), "*In vivo* administration of EGF directly into the adult mouse subventricular zone has a greater effect on the frequency of neural progenitors than neural stem cells (Keystone 2005)," available at http://www.stemcell.com/technical/keystone05_NCFC.pdf. For the convenience of the Examiner, a copy of this article is enclosed herewith as Exhibit H.

(E) Weiss Teaches Away From The Method of the Amended Claims

One of ordinary skill in the art reading Weiss would not have been motivated to select extra-ventricular administration or TGF-α or the two in combination, as recited in the amended claims, when confronted by the many options presented by Weiss together with specific working examples using EGF, FGF or a combination of them set out in Weiss.

The skilled worker would have believed those Examples to work for their intended purpose. When they did not -- a fact unequivocally demonstrated by Dr. Fallon's experiments described above and confirmed by the work of others -- the skilled worker would not know where to turn among all of the other possible growth factors and modes of administration set forth in laundry-list like fashion in Weiss. *See In re Omeprazole Patent Litig.*, 536 F.3d 1361 (Fed. Cir. 2008) (holding claimed drug formulation non-obvious where one of ordinary skill in the art would not have recognized that the prior art drug formulation did not work, and therefore would not have been motivated to change the prior art formulation to make the claimed formulation, and even if one of ordinary skill had recognized that the prior art formulation did not work, one of ordinary skill in the art had many options that would not have led to development of the claimed formulation, including dropping the project).

Moreover, Weiss teaches away from the method of the amended claims, by focusing on intracerebroventricular administration of EGF or FGF, not the claimed TGF-α and extra-ventricular administration. *See In re Baird*, 16 F.3d 380, 382 (Fed. Cir. 1992) (holding prior art reference taught away from a selected species by focusing on other species in genus); *see also In re Marosi, Stabenow, and Schwarzmann*, 710 F.2d 799 (Fed. Cir. 1983) (holding process claims reciting "free of alkali metal" not obvious where alkali metal component taught as essential ingredient was excluded, because one of ordinary skill in the art would expect that absence of essential ingredient would yield undesirable or no reaction). The only "working" examples of *in vivo* administration in either Weiss or Reynolds recite intracerebroventricular administration of EGF (in the presence or absence of FGF-2). *See* Weiss at Example 27.

Accordingly, Weiss teaches away from the claimed methods, drawn selectively to the combination of extra-ventricular administration and **TGF-α**.

(F) Conclusion

For all of the above reasons, Weiss alone, or together with Kelly, does not make obvious the methods of the amended claims.

There is no reason why one of ordinary skill in the art reading Weiss would choose TGF-α as the growth factor to administer, or why they would select administration of the **TGF-α** outside of the ventricles and to a location selected from the group consisting of the striatum, pallidum, septem, cortex, external capsule, substantia nigra-ventral tegmentum and at a site adjacent to an ependymal and subependymal zone or why they would do both in combination. Indeed, they would have had no reason to modify Weiss's examples.

The non-obviousness of the amended claims is further supported by the evidence of the surprising results obtained by the claimed extra-ventricular administration of TGF-α, including substantial cell proliferation, directed cell migration, neurogenesis and behavioral improvement demonstrating functional recovery. By contrast, the FGF and EGF of Weiss, whether administered to the ventricles or to the striatum, do not induce substantial cell proliferation, directed migration or functional recovery.

Double Patenting

Claims 1, 5, 6, 33, 63, 65 and 70-73 stand provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being allegedly unpatentable over formerly co-pending United States patent application 09/129,028 (now US patent 7,790,669) and 10/167,384 (now US patent 7,795,202).

Applicant requests that this rejection be held in abeyance until allowable subject matter is found in the instant application. Applicant will then respond to the obviousness-type double patenting rejection in the appropriate way, *i.e.*, by argument or by the filing of the appropriate Terminal Disclaimer.

CONCLUSION

In view of the amended claims, the above arguments and the Fallon II Declaration and Exhibits A-I, applicants request allowance of the amended claims. The Examiner is invited to telephone the undersigned at (212) 596-9034 for any reason to advance the prosecution of the application.

Respectfully submitted,

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